EXHIBIT 2

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By Tracy J. Dr...

PATENT

Attorney Docket No. 11823-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
NICHOLAS F. LANDOLFI	Examiner: DRAPER
Serial No.: 07/532,267	Art Unit: 1812
Filed: 1 June 1990	AMENDMENT
For: CHIMERIC LIGAND/IMMUNOGLOBULIN MOLECULES AND THEIR USES	

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action dated 23 March 1992, Applicants respectfully request reconsideration and reexamination of the claims of the above-identified application in view of the following amendments and remarks.

AMENDMENTS

IN THE TITLE

Please delete the title and replace therefor the following replacement title:

--Immunoligands Comprising An Immuoglobulin Constant Region Component and a IL-2 Receptor Binding Component--

IN THE SPECIFICATION

On page 4, line 2, delete "growth factor-like moiety" and substitute therefor --growth factor amino acid sequence--.

IN THE CLAIMS

1.(amended) An immunoligand comprising a ligand component linked in peptide linkage to an immunoglobulin constant region component comprising an immunoglobulin domain, and wherein

a1 and/or B

the ligand component comprises an amino acid sequence of interleukin-2 capable of binding an interleukin-2 receptor and the immunoligand is capable of binding to a cell surface receptor through the ligand component.

a2 and/or B

5.(amended) An immunoligand of claim 1, wherein the ligand component is linked to the constant region component via a peptide bond to a hinge region of said constant region component.

a3

9.~~(amended)~~ An immunoligand of claim 8 wherein the ligand component comprises [an amino acid sequence of interleukin-2 capable of binding an] a human interleukin-2 [receptor] protein.

11.(amended) An immunoligand comprising a growth factor amino acid sequence [-like moiety] linked in peptide linkage to at least one domain of an immunoglobulin heavy chain constant region, wherein the growth factor amino acid sequence [-like moiety] is capable of binding to a cell surface receptor.

12.(amended) An immunoligand of claim 11 wherein the [ligand component] growth factor amino acid sequence is [linked to the constant region component by a peptide bond] a naturally-occurring peptide or protein molecule.

a4

13.(amended) An immunoligand of claim 12 comprising [a lymphokine-like moiety] an interleukin-2 amino acid sequence linked in peptide linkage to at least one domain of an immunoglobulin heavy chain constant region wherein the [growth factor-like moiety] immunoligand is capable of binding to a cell surface interleukin-2 receptor.

14.(amended) An immunoligand of claim 12 wherein the heavy chain constant region is a human IgG1 heavy chain constant region.

a5

23.(amended) A pharmaceutical composition comprising a suitable carrier and an immunoligand of claims 1 or 12, wherein the immunoligand binds to an interleukin-2 receptor.

B

Amended claims 1, 5, 9, 11-14, and 23, and original claims 2-4, 6-8, 10, and 15 are pending. Applicant respectfully requests that the Examiner enter the amended claims.

10-17

REMARKS

Before addressing the rejections raised by the Examiner, it is appropriate to briefly discuss the claimed invention. The invention as now claimed comprises immunoligands, which are chimeric proteins comprising a polypeptide hormone or growth factor sequence that binds to a cell surface receptor linked, in peptide linkage, to an immunoglobulin constant region component comprising an immunoglobulin constant region domain. As now claimed, the invention relates to immunoligands which bind to the inteleukin-2 (IL-2) receptor, which are not described and enabled by the cited references.

Objection to the Title and Specification

The Examiner has objected to the title as being insufficiently descriptive. Applicant has amended the title to more closely describe the claimed invention.

The Examiner has also objected to the Specification under 35 U.S.C. §112, first paragraph as being a description of an invention which is inoperative, non-enabling, and lacking patentable utility. The Examiner has requested a deposit of a cell producing the exemplified embodiment. The Applicant believes that the example provided in the Specification, beginning on page 18, line 10 and continuing to the end of the Specification is sufficiently detailed, indeed more than sufficiently detailed, to permit one of skill in the art to practice the invention. Each component listed in the Specification on page 18, beginning on line 19, is readily available to those of skill in the art in polynucleotide form, or as a GenBank or other published polynucleotide sequence which can be readily interconverted into polynucleotide form by making (and ligating if necessary) synthetic oligonucleotides on the basis of the sequence data. Given these components, the construction of vectors, transfection, purification of the immunoligand, and its usage is described in more than sufficient detail to permit those of skill in the art to prepare and purify an immunoligand that binds to the IL-2 receptor. Therefore, the Specification describes the invention in sufficient detail to be enabling, and

the exemplified embodiment is shown, in the Specification to be operative in producing the immunoligand. The Examiner's requirement for deposit is respectfully traversed, as the invention is fully enabled by the detailed description of the exemplified embodiment.

As to the Examiner's contention that the invention lacks patentable utility, Applicant directs the Examiner's attention to the following excerpts from the Specification as proof of patentable utility:

On page 23, lines 22-29:

> The chimeric molecule was capable of stimulating proliferation of the CTLL cell line, and comparison with the proliferation stimulated by recombinant human IL-2 revealed that on a per molecule basis, the chimeric IL-2/IgG1 has a specific activity indistinguishable from recombinant human IL-2 (Fig. 4a). Thus, the IL-2 moiety of the chimeric molecule is in a fully functional configuration, exhibiting both the binding and proliferation-mediating activities of IL-2.

On page 23, lines 35-37:

> IL-2/IgG1 was compared with the murine anti-Tac monoclonal antibody for the ability to mediate complement-dependent lysis of the HuT-102B cell line.

On page 24, lines 14-16:

> IL-2/IgG1 has the ability to specifically lyse HUT-102B cells in the presence of complement, although at a somewhat less efficient level than does anti-Tac (Fig. 4b).

On page 24, lines 20-29:

> IL-2/IgG1 was also examined for the ability to mediate ADCC. The murine anti-Tac monoclonal does not mediate ADCC, however the chimeric and humanized versions of this antibody exhibit detectable levels of ADCC activity with the use of an activated effector cell population (Junghans, et al., supra. IL-2/IgG1 and chimeric anti-Tac each exhibited a small (28% and 15%, respectively) enhancement of lysis of HuT-102B target cells in a four hour assay. In conclusion, these results indicate that the IL-2/IgG1 molecule possesses the functional activities of both the IgG and IL-2 moieties.

Applicant believes that the demonstration of the efficacy of the immunoligand in the complement-dependent lysis assay and the ADCC assay demonstrates patentable utility. The Examiner is reminded of the recent Board decision in Ex Parte Aggarwal, 23 USPQ2d 1334 (BPAI, 1992), copy enclosed, wherein the Board staes, on p.1339:

> Case law subsequent to Brenner is receptive to early filing of applications in the biomedical field so long as the patent applicant, when properly challenged by the examiner, can provide evidence showing substantial activity in screening tests customarily used and accepted as predictive of human activity for the type of chemical tested. Of course, the evidence presented must be commensurate with the scope of utility asserted and the subject matter claimed.

Applicant submits that the complement-dependent lysis assay and the ADCC assay results using the IL-2 immunoligand are sufficiently predictive of its biological and immunological activities to indicate that the invention possesses patentable utility in accordance with Ex Parte Aggarwal. Applicant therefore requests that the Examiner withdraw the objection to the Specification as describing an invention that lacks patentable utility.

Rejection Under 35 U.S.C. §§101 and 112, First Paragraph

The Examiner has rejected Claims 1-15 under 35 U.S.C. §112, first paragraph as describing an invention that is non-operative, non-enabled, and lacking patentable utility for the reasons cited in the objection to the Specification. Claims 1-15 and 23 were rejected by the Examiner under 35 U.S.C. §§101 and 112, first paragraph, as being nonenabling without a deposit being made. For the reasons cited above, the detailed exemplification in the Specification and the assay results, and the amendments to the Claims, Applicant respectfully requests that the Examiner withdraw the rejection.

Rejection Under 35 U.S.C. §112, First and Second Paragraphs

The Examiner has rejected Claims 1-15 under §112, first and second paragraphs for being an allegedly non-enabling description and for failing to point out and distinctly claim the

invention. Claims 1-7 and 23 were rejected as broad and indefinite for use of the word "ligand component". Although the term "ligand component" is described in the Specification on page 3, lines 33-37, and described and exemplified with multiple examples on page 7, lines 7-32, Applicant has amended the Claims to clarify the term further. Claims 1, 5-7, and 23 were rejected as broad, indefinite, and confusing in the term "constant region component". The term "constant region component" is defined in the Specification, on page 6, lines 29-34, and the Claims have been amended to clarify the term further. Claims 11-14 and 23 were rejected as broad, indefinite, and confusing in the use of "growth factor-like" and "moiety". As amended, these claims no longer use the term "growth factor-like" or "moiety".

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected Claims 4 and 12-14 under §112, second paragraph as being indefinite. The Examiner rejected Claim 4 as reciting improper Markush language. Respectfully, Claim 4 is not a Markush claim, indeed it is more limited in that it recites that the constant region component consists of all of the elements: hinge region, C_H2 domain, and C_H3 domain. The rejection of Claim 12 and Claim 13 for the cited language has been addressed by amendement of the claims. Claim 14 has antecedant basis for "the heavy chain constant region" in that Claim 14 depends from dependent Claim 12 which draws antecedant basis for the term from Claim 11.

Rejections Under 35 U.S.C. §§102(a), 102(b), and 103

The Examiner has rejected Claims 1-2 and 6-7 under 35 U.S.C. §102 (a or b) or, in the alternative §103, in view of the cited Traunecker et al., Schnee et al., and von Wussow et al. The cited art is readily distinguished from the present invention as now claimed, and discussion of the cited art is not an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention.

Traunecker et al. describes making an immunoglobulin chain having a portion of the CD4 sequence replacing the V and

C_H1 domains of γ2a or μ chains. The immunoglobulin chains made by Traunecker et al. bound a free viral glycoprotein, gp120, but were not reported to either: (1) bind to a cell surface receptor, such as an Il-2 receptor, or (2) to possess biological activity as defined by complement-mediated lysis, ADCC activity, or IL-2 activity. Therefore, Traunecker et al. neither anticipates nor makes obvious the claimed invention.

Schnee et al. reports a heavy chain-tPA fusion polypeptide having a fraction of the peptidolytic tPA activity of native tPA. The fusion protein reported by Schnee et al. did not: (1) bind to a cell surface receptor, such as an IL-2 receptor, (2) have demonstrated complement-mediated lysis, ADCC activity, or IL-2 cytokine activity. Therefore, Schnee et al. neither anticipates nor makes obvious the claimed invention.

Von Wussow et al. disclose making an immunoconjugate wherein a purified α-interferon molecule is linked to an immunoglobulin molecule by a non-peptide chemical linkage. The non-peptidyl linkage of two purified proteins differs from the claimed invention in several respects. First, the effector functions of the immunoglobulin in the von Wussow conjugate were not shown to be elicited (and would not be expected) by binding of α-interferon to its receptor, whereas Applicants IL-2 immunoligand has demonstrated effector functions upon binding (e.g., complement-mediated lysis). Second, von Wussow does not show that the α-interferon conjugate is able to target cells bearing a α-interferon receptor and mediate ADCC. Finally, the immunoconjugate of von Wussow does not indicate that one of skill in the art would have a reasonable expectation of success in making the IL-2 immunoligand of the Applicant's invention, which is biologically active as a cytokine and has ADCC and complement-mediate lysis activity, which are not predicted by von Wussow. Therefore, von Wussow et al. neither anticipates nor makes obvious the claimed invention.

Therefore, Applicant submits that the invention, as now claimed, is not anticipated under §102 (a or b) and is not obvious under §103.

Summary

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 326-2400.

Respectfully submitted,

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